Abstract

The clinical investigation outlined in this protocol are designed to test the hypothesis that direct intramyocardial injections of naked DNA encoding for vascular endothelial growth factor ($phVEGF_{165}$) in patients with advanced heart failure is safely tolerated and may in some patients lead to improvement in their clinical status.

The clinical trials that we have proposed incorporate a strategy that is designed to address patients in whom all medical measures to treat advanced congestive heart failure (CHF) have failed, leaving these patients in need of cardiac transplantation. Owing to the mismatch that currently exists between the number of patients in need of cardiac transplantation and the number of available donors, implantation of a left ventricular assist device (LVAD) is often required for patients as a so-called "bridge" to transplantation. It is this population of patients-those undergoing LVAD implantation for advanced heart failure-that are intended to be addressed in the current protocol. For the purpose of our clinical studies, these patients have been divided into two large subgroups, based on associated evidence of intramural coronary artery disease (CAD). Accordingly, the objectives of the protocol are as follows:

1. **Objective #l:** To evaluate the safety and impact of $phVEGF_{165}$ gene transfer on LV function in patients with CHF due to coronary artery disease.
2. **Objective #2:** To evaluate the safety and impact of $phVEGF_{165}$ gene transfer on LV funciton in patients with CHF due to idiopathic dilated cardiomyopathy, excluding patients with significant narrowing of the extramural coronary arteries or primary valvular heart disease.
3. **Objective #3**: To evaluate the efficacy of $phVEGF_{165}$ gene transfer to allow for LVAD bridge-to-recovery (BTR) as an alternative to transplantation.

The protocol outlined in this Investigational New Drug Application has been designed as a PhaseI/PhaseII, single-site, dose-escalating, double-blind, placebo controlled study to evaluate the safety and impact of $phVEGF_{165}$ gene transfer to promote angiogenesis in patients with advanced heart failure. Males of females >21 years with diagnosis of ischemic cardiomyopathy requiring LVAD implantation will be eligible. A total of 144 patients (72 patients for each of 2 study arms) will be recruited over a period of 4 years (the fifth year will be limited to follow-up examinations). The 72 patients in each arm of the study will comprise 3 cohorts, each consisting of 24 patients. Within each of these cohorts, patients will be randomized to receive $phVEGF_{165}$ or placebo based upon a 3:1 randomization ratio. Thus, at the completion of the study, 18 patients will have each received a given dose (125, 250, or 500 ug $phVEGF_{165}$) and 18 patients will have received placebo. Doses will be employed in a serial dose-escalating fashion. The entire volume of the study drug will be divided and delivered in 4 intramuscular injections administered into the left ventricular wall and the distribution of the territories of the left anterior descending (2 injections), circumflex territory (1 injection), and right coronary artery distribution (1 injection).